REMARKS

The Office Action of December 20, 2001 presents the Examination of claims 52-73 and 76-79. These claims remain pending. New claims 80-82 are added. These claims are identical to pending claims 60-62, but dependent from claim 53, rather than from claim 52. Thus, no new matter is added by the new claims. Minor editorial amendments are made to claim 62.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 52-73 and 76-79 stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement of the claimed invention by the specification. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

As a threshold matter, the Examiner agrees that claims to compositions limited to the specific Ad-rsvLuc constructs specifically exemplified in the specification are enabled. The Examiner points out in particular that viral vectors having significant regions of the adenoviral vector and the mlc-2 promoter sufficient to achieve the results unexpected in view of Buttrick that Applicants have previously argued. The Examiner

also indicates that methods for gene delivery by direct cardiac injection are also enabled by the specification.

In this regard, the Examiner is reminded that the previously pending claims 53, 55, 57, 58, 59 and 78 recite structural limitations, i.e. specific portions of the Mlc-2 promoter that confer cardiac tissue-specific expression upon a vector that the Examiner is requiring. Claims 61-63 recite adenovirus or adenovirus-associated vectors, or the part thereof important for operability (the ITRs that provide for insertion of the transgene into the infected cell genome), thus including the vector limitation required by the Examiner. Accordingly, at least these claims should be free of the instant rejection. New claims 80-82 recite both the specific promoter portions and the adenovirus or adeno-associated virus vectors and so these claims should also be free of the instant rejection.

As to the method claims, claim 69 recites administration to cardiac tissue. Thus, claim 69, and claims 70 and 71 dependent therefrom, still include a limitation that the vectors are delivered to the heart. Direct injection into the muscle of the heart is not required for operability of the invention, as explicitly demonstrated by Example 8 (page 21 of the specification), showing administration to the heart cavity. Thus, limitation of the method claims to injection directly into

heart muscle is not required for enablement and at least claims 69-71 should be free of the instant rejection.

As to the remaining claims, the Examiner bases the rejection entirely on an assertion of unpredictability in achieving the results of the present invention. The Examiner takes a position that, because Applicants asserted unpredictability in achieving cardiac-specific expression, trial and error experimentation must be performed to determine if any embodiment of the invention is operable.

First, Applicants submit that the Examiner has failed to make the required *prima facie* case of lack of enablement necessary to support her rejection of the broader claims. Enablement is a question of whether undue experimentation is required to practice the invention throughout the scope of the claims. *In re Wands,* 8 USPQ2d 1400 (Fed. Cir. 1988) lists eight factors that must be considered in weighing whether undue experimentation is required to practice the invention:

1. the quantity of experimentation necessary;

2. the amount of direction or guidance provided [by the specification];

3. the presence of working examples;

4. the nature of the invention;

5. the state of the prior art;

6. the relative skill of those in the art;

7. the predictability or unpredictability of the art; and

8. the breadth of the claims.

See Wands at page 1404.

Wands makes the further point that enablement is not a question of whether experimentation is required to determine operability of various embodiments of the invention, but rather of whether undue experimentation is required. Thus, the Court found that, in arts where experiments such as screening embodiments for operability is expected by the skilled artisan to have to be performed, and where the necessary screens are either described in the specification or known in the prior art, then such screening experiments are not undue experimentation. (*See Wands* at p. 1406).

It is manifestly apparent that the Examiner improperly relies entirely upon the unpredictability factor in making the instant rejection. While the logic of asserting unpredictability in achieving certain results in view of prior art, which results show unobviousness of the invention, is attractive, such logic is not legally sufficient by itself. The Examiner must go on to consider the other seven factors for weighing whether experimentation needed to practice the invention is well-described, within the skill of the artisan,

and expected to have to be performed by the skilled artisan. Applicants present their views on these issues below.

Quantity of Experimentation

The quantity of experimentation required to determine whether an embodiment of the present invention is typical of the art. As noted above, many of the rejected claims expressly recite particular portions of the Mlc-2 promoter to be used to confer cardiac-specific expression to the operably-linked structural gene. The operability of such embodiments has already been confirmed as described in the specification. Thus, little or no experimentation is required to determine operability of the embodiments with claims 53, 55, 57, 58, 59 and 78 and claims dependent therefrom.

As to claim 52, and claims dependent therefrom, these claims recite that a regulatory portion of the Mlc-2 promoter effective to confer cardiac-specific expression should be employed. The experimentation required to test a particular embodiment is the creation of an expression vector comprising a part of the Mlc-2 promoter, which promoter has been identified in the present specification, and examining expression of the structural gene portion of the construct in either cultured cardiac cells and cultured cells of other tissue, or by

administration of the vector to an animal model organism, such as a mouse, by methods described in the specification. Then, the specificity of expression of the structural gene must be examined by some method, perhaps by Northern blotting of RNA from the cultured cells or tissues of the animal, or by Western blotting of the expressed proteins. All of the techniques for performing these experiments are either described in the specification or known in the art. Applicants' Representative supposes that, given clones of the Mlc-2 gene, perhaps four to six weeks' work might be necessary to accomplish these experiments. If a new Mlc-2 gene is to be isolated, that might add one to two weeks of work to the task.

Amount of Direction or Guidance

The amount of direction or guidance provided by the instant specification is considerable. The nucleotide sequence of the Mlc-2 promoter from a mammalian organism is provided (SEQ ID NO: 1). Description of working vectors is provided (Figures 1 and 2). A reporter gene useful for monitoring promoter function (luciferase) and an example of its use to determine efficacy of various parts of the upstream region of two genes (light chain and heavy chain) in conferring cardiac-specific expression is described (Examples 1-12). At pages 4-5 of the specification,

particular portions of the Mlc-2 promoter that merit attention are described, and the idea that a mammalian promoter is preferred is also set forth. At page 10, the specification provides description of how useful regulatory sequences can be isolated from various mammalian genomes. These portions of the specification provides detailed guidance as to what DNA is likely useful for providing cardiac-specific expression.

As to the vector to be employed, at pages 6-7, adenovirus vectors and adeno-associated vectors are described in detail. This portion of the specification also guides the artisan toward the use of the minimal portion of the adenovirus needed for insertion of the desired gene into the genome of the subject, the ITRs.

Presence or Absence of Working Examples

The specification provides 12 working examples illustrating each step of the invention, from construction of various expression vectors utilizing different portions of two different promoters, through testing of the embodiments in cell culture for promoter function to *in vivo* comparative testing of different embodiments in a mouse model system. These working examples amply describe the experimentation that should be

performed to determine if any particular embodiment is operable to produce cardiac tissue-specific expression of a desired gene.

Nature of the Invention

The present invention relates to expression vectors for obtaining cardiac-specific expression of a desired gene, and to methods for utilizing such vectors to effect expression of a desired gene specifically in the heart tissue of an animal.

The State of the Prior Art

The state of the prior art at the time the invention was made was such that cloned DNA from rodents that encompassed the Mlc-2 promoter was known. Furthermore, the ability of that promoter to drive expression of a gene in cultured cells had been examined. Also, methods for dissecting promoters to determine how particular portions of them affect transcription in cultured cells were known, e.g. deletion experiments utilizing reporter genes.

The state of the art at the time the invention was made was such that expression of a desired gene in different types of cultured cells was not particularly predictive of expression patterns in tissues of a whole animal.

Relative Level of Skill in the Art

The relative level of one of skill in the art of recombinant DNA technology is considered very high. The typical artisan will have an advanced degree, often a Ph.D. and/or M.D. and will have experience in the design and implementation of complex experiments involving tissue culture and/or animal subjects.

The Predictability of the Art

The predictability of the art is indeed low in certain aspects. However, the Examiner has incorrectly applied Applicants' argument regarding the inability of one skilled in the art to predict the pattern of expression obtained in tissues of whole animals from results in the prior art, which unpredictability was one basis for withdrawal of a prior art rejection, to the question of enablement of the claimed invention.

In particular, Applicants have demonstrated by experimental results that the tissue specificity of expression of a structural gene from upstream elements of the Mlc-2 promoter is different when that construct is administered to somatic cells by a vector from when a similar construct is introduced into a genome by injection of the construct into oocytes. However,

these unpredictable differences in expression due to the state of the organism into which the construct is introduced (an undifferentiated gamete compared to an adult animal) do not necessarily imply that it is unpredictable that the same construct, introduced into cells of an adult animal by different viral vectors, will behave differently. Nor do such results imply that "trial and error" experimentation is necessary to select the portions of an Mlc-2 promoter that are effective to produce cardiac tissue-specific expression of a desired gene. That is, as in the present instance, once the portions of the Mlc-2 promoter that are effective to produce cardiac tissue-specific expression of a desired gene in somatic tissues of an adult animal have been identified, that information can predictably guide further experimentation to identify homologous segments in Mlc-2 genes from other organisms, or to identify homologous segments in other genes from the same organism.

Indeed, the attached second Declaration of Dr. Franz describes the identification of the human homolog of the rat Mlc-2 promoter described in the specification and provides his opinion that it is the particular portions of the promoter, not the particular vector used to introduce the construct into the tissues of the animal, that drive tissue specificity of gene expression. Dr. Franz reaches this conclusion on the basis of

data from an experiment described in the specification in which the tissue specificity of the Mlc-2 promoter is compared to that of the α-Mhc promoter when constructs of each are introduced into mice using the same adenovirus vector to make the constructs.

The Breadth of the Claims

As explained above, many of the rejected claims recite the very limitations that the Examiner has suggested are necessary to conform the scope of the claims to the scope of enablement by the specification. The broader claims are claims 52 and those dependent therefrom. Claim 52 recites that at least one regulatory element of the 5′ portion of a myosin light chain 2 gene should be included in the promoter that drives expression of the nucleic acid sequence to be expressed. Claim 52 further includes a functional limitation that the regulatory sequence must be effective to provide cardiac tissue-specific expression of the sequence to be expressed.

When all of the factors that must be considered when determining whether undue experimentation is required for the skilled artisan to practice the present invention throughout its scope are in fact considered, it is clear that the present claims are enabled by the present specification.

Finally, the Examiner also repeatedly asserts that "trial and error" experimentation is necessary for one to practice the present invention as broadly as claimed. Even if one might choose to ignore the eight factors enumerated above, the standard for experimentation that defines lack of enablement is undue experimentation. As the Court in *Wands* held, such experimentation as is expected in the art to be necessary to practice an invention broadly is not undue experimentation. Thus, if "trial and error" experimentation is expected to have to be performed by the skilled artisan to practice the present invention broadly, and if the trials which constitute such experimentation are described in the specification or known in the prior art, then even such "trial and error" experimentation is not undue experimentation.

For all of the above reasons, Applicants assert that the present specification well enables practice of the claimed invention. Accordingly, the instant rejection of claims 52-73 and 76-79 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement of the claimed invention by the specification, should be withdrawn.

Applicants submit that the present application well-describes and claims patentable subject matter. The favorable

action of allowance of the pending claims is respectfully requested.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition(s) for a three (3) month extension of time for filing a reply in connection with the present application, and the required fee of $460.00 is attached hereto.

If there are any minor matters precluding allowance of the application which may be resolved by a telephone discussion, the Examiner is asked to contact Mark J. Nuell, Ph.D. (Reg. No. 36,623) at (703) 205-8000.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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Attachments: **Mark-up version showing changes**
Declaration
Exhibits 1 and 2

VERSION WITH MARKINGS TO SHOW CHANGE MADE

IN THE CLAIMS

Claim 63 has been amended as follows:

63. (amended) The recombinant virus vector according to claim 62, wherein said replication deficient adenovirus vector consists of two inverted terminal [repetition] repeat sequences (ITR) of said adenovirus.

Claims 80-82 have been added.